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(71) Applicant: ATP AVANT-GARDE TECHNOLOGIES & PRODUCT MARKETING & LICENSING S.A. [CH/CH]; Via Pizzamiglio, 12, CH-6833 Vacallo (CH).

(72) Inventor: BADETTI, Rolando; Via Guerrazzi, 49, I-20052 Monza (IT).

(74) Agent: RICCARDI, Sergio; Riccardi & Co., Via M. Melloni, 32, I-20129 Milano (IT).

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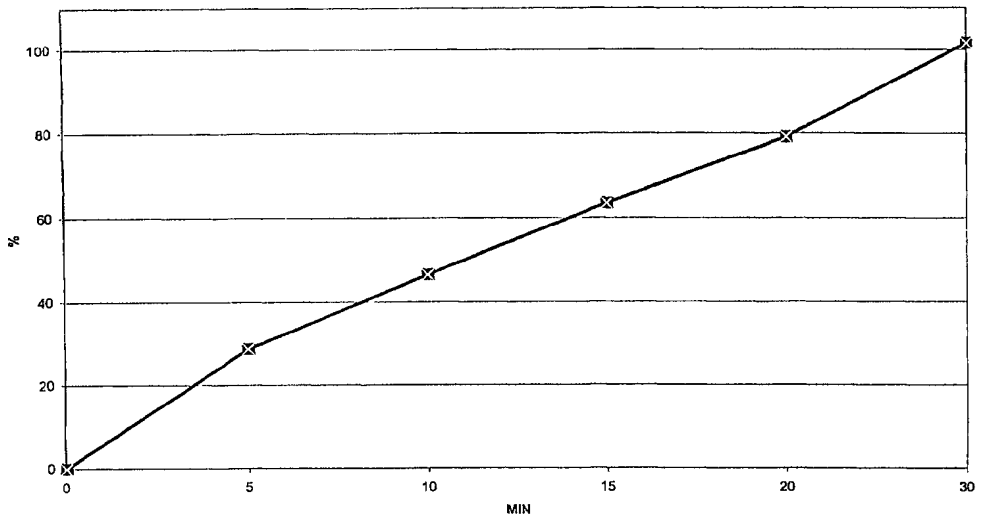
(54) Title: COMPOSITION FOR MEDICATED CHEWING GUMS, PROCESS FOR MANUFACTURING THE SAME AND TABLETS SO OBTAINED



(57) Abstract

A composition for medicated chewing gums having the active principle dispersed in the gum and coated by a mixture consisting of a hydrosoluble element and a water insoluble one. The principle can be one or more from the group consisting of nicotine, ibuprofen, paracetamol, D-metorfan, dimenhydrinate, ginger, l-ascorbic acid (vitamin C), acetylcysteine, ephedrine, D-pseudoephedrine, valerian, ranitidine, chlorexidine, tibenzonium iodide, preferalby nicotine while the soluble element is a carbohydrate, preferably sorbitol and the water insoluble element is an oil, preferably hydrogenated castor oil. A process for manufacturing a tablet of medicated chewing gum having the composition according to the invention is also described. The tablet according to the invention has high stability organoleptic properties and gradual and controlled release properties.

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"COMPOSITION FOR MEDICATED CHEWING GUMS, PROCESS FOR MANUFACTURING THE SAME AND TABLETS SO OBTAINED"

The present invention relates to a composition comprising a therapeutically active principle for use in medicated chewing gums. The present invention relates particularly to a composition for medicated chewing gums comprising nicotine.

As the chewing gums have reached high popularity and compliance since the beginnings of this century, chewing gums containing a therapeutically active principle in particles dispersed in the gum and defined "medicated chewing gums" have been developed.

The problems associated with such gums are numerous such as the reproducibility of the release rate of the active principle from the gum, the stability and the masking of the unpleasant taste of the active substance and so on.

These problems were attempted to be solved first of all by using micro-encapsulation techniques which resulted not completely satisfactory because of the delay of the active principle release from the gum. Good results have been achieved by encapsulating such active principles in compounds suitable to include them such as the cyclodextrins and producing the gums with cold-pressing techniques. Such method serves to preserve the stability of the active principle and solve some of the above-noted technical problems.

None of these solutions allowed to solve another problem associated with chewing gums i.e. the feeling of irritation deriving from the contact of the therapeutically active principle with the mucous membrane (mucosas) of the oral cavity, a situation which is particularly annoying when the active principle has irritant properties, as in the case of nicotine.

An attempt at solving this problem is described in French patent 7 340 760 wherein a composition comprising a buffer system suitable to increase the physiological pH of the mouth mucous membrane, decreasing the irritant sensation of the mouth generated by the chewing gums comprising nicotine.

Therefore it is an object of this invention to provide a chewing gum composition in order to attain a gradual and controlled release of a

therapeutically active principle which does not use a system altering the mouth pH, but which, however, avoids the throat irritation generated by the therapeutically active principle, while maintaining a high absorption thereof.

Another object of the present invention is to provide a chewing gum comprising a therapeutically active principle which has high heat and humidity stability and high organoleptic properties.

It is still an object to provide an easy process which allows a chewing gum having high stability and organoleptic properties to be obtained.

It is still another object to provide a chewing gum comprising an active principle which allows the masking of the possible unpleasant taste generated by the same active principle.

The objects cited above are achieved by providing a composition with the characteristics stated in claim 1 and obtained by the process stated in claim 19. The advantageous properties of the composition of the present invention are achieved providing for the characteristics stated in dependent claims.

The composition according to the invention is characterized by the fact that an active principle which is dispersed in the gum is coated by a mixture comprising a water insoluble element and a hydrosoluble element.

The invention is also directed to formation of the composition into a tablet of medicated chewing gum wherein said tablet is stable at 40°C and 75% humidity for 6 months.

The invention is also directed to a method of administering nicotine to a person through the oral cavity (for example, in order to treat the person to give up smoking) wherein the method comprises administering the gum of the invention.

The coating mixture of the active principle of the invention is such that the hydrosoluble element dissolves in contact with saliva during the chewing function, generating particular pathways for the exit of the active principle, whereas the insoluble element remains in the gum. In such a way the active principle comes out and contacts the mouth mucous membranes, whereas the coating mixture remains in the gum.

The composition of the invention will be detailed together with the preferred illustrative embodiments not limiting the invention and the Figure,

which is a plot of the release curve of the active principle of a tablet according to the invention obtained through HPLC (High Pressure Liquid Chromatography) analysis.

The insoluble element according to the invention is an oil or other insoluble substance, preferably selected from the group consisting of plant hydrogenated oils, paraffin, beeswax, stearic alcohol , stearyl alcohol, cetyl alcohol, cetostearyl alcohol, more preferably hydrogenated castor oil.

The soluble element is a carbohydrate or a polyhydric alcohol preferably selected from the group consisting of sorbitol, sucrose, lactose, glucose, fructose, mannitol, xilitol, isomalt, more preferably sorbitol.

The active principle contained in the chewing gum according to the invention can be selected from the group consisting of nicotine, ibuprofen, paracetamol, D-metorfan, dimenhydrinate, ginger, 1-ascorbic acid (vitamin C), acetylcysteine, ephedrine, D-pseudoephedrine, valerian, ranitidine, chlorexidine, tibenzonium iodide. A preferred active principle according to the invention is nicotine in the form of nicotine polyacrylate in amounts between 0.1 and 20% by weight, preferably 1.1% by weight (11.11 mg of the total formulation). Such a composition comprising nicotine is suitable for the use in the treatment for giving up smoking.

If the amount of the active principle is defined as Z, then the insoluble element is between 1Z and 10Z and the soluble element between 2Z and 20Z. In other words, the insoluble element is present in the ratio of from 1 to 10:1 of the active principle, and the soluble element is present in the ratio of from 2 to 20:1 of the active principle. The composition according to the invention comprises as active principle nicotine polyacrylate in amounts of 1.11% by weight of the total composition, therefore the insoluble element will be between 1.11% and 11.1% by weight, preferably 6%, while the hydrosoluble element between 2.22% and 22.2%, preferably 10% by weight of the total composition.

As a matter of fact from the tests of *in vitro* release carried out for 30 minutes it was shown that if the insoluble element is below 1.1% then the release of nicotine increases at 5 and 10 minutes, remaining similar at higher times, while above 11.1% the release of nicotine decreases at 5 and 10 minutes and remains similar at subsequent times and that if the soluble

element is below 2.22% the release is slower and incomplete, while above 22.2% the release is complete but quicker.

The composition of the invention preferably comprises nicotine as active principle, hydrogenated castor oil as insoluble element and sorbitol as hydrosoluble element, preferably in amounts of 1.1%, 6% and 10% by weight of the total composition, respectively.

The composition of the invention comprises a gum base which is selected each time according to the health regulations of the countries where the product is consumed. For instance, the gum base in the present invention may comprise any suitable gum base material known in the art, including natural gum bases, such as chicle, jelutong, gutta percha and crown gum or synthetic gum materials such as butadiene-styrene rubber, isobutylene-isoprene copolymer, paraffin, petroleum waxes, polyethylene, polyisobutylene polyvinyl acetate, or blends thereof. In a preferred embodiment, the gum base comprises synthetic gum base materials.

The gum base composition may comprise from about 5 to 25%, preferably from about 10 to 18% by weight elastomers; from about 25 to 55% preferably from 38 to 48% by weight resins, from about 15 to 40% preferably from about 22 to 32% by weight plasticizers; from about 10 to 25%, preferably from about 13-16% by weight water insoluble adjuvants; and from about 0.05 to 0.1% preferably about 0.1% by weight food grade anti-oxidants.

The gum base for use in the invention may be prepared by cooling the gum to -30/-40°C and grinding it.

The composition according to the invention can also contain additives among which flavours, sweeteners, dehydration agents, pH stabilizers, inclusion agents, lubricants, compression adjuvants, etc can be mentioned.

Flavouring agents suitable for use in the invention include essential oils and synthetic flavours such as citrus oils, fruit essences, peppermint oil, spearmint oil, clove oil, oil of wintergreen, anise and the like. Artificial flavorants known to those skilled in the art are also contemplated for use in the invention.

Compression adjuvants may also be added. These compounds facilitate compression of the gum into tablets. Suitable compression

adjuvants include silicon dioxide, magnesium stearate, behenic acid, talc and similar substances. Compression adjuvants are often essential to limit the tendency of the gum tablets to stick to the presses during manufacture.

The sweeteners according to the invention are preferably selected from the group consisting of acesulfame K, aspartame, saccharin, cyclamates, neoesperidine, maltol, ethylmaltol.

The pH of the composition will be between 5 and 10, preferably 7.5.

The chewing gum according to the invention is obtained with the process consisting of the following steps:

a) heating the insoluble element until a complete solution is obtained;

b) mixing the soluble element with the active principle;

c) pouring the mixture of step b) in the solution of the insoluble element;

d) cooling the mixture so obtained and mixing with the gum base and the additives; and

e) pressing at a temperature not above room temperature.

The active principle is preferably nicotine, the insoluble element is hydrogenated castor oil and the soluble element is sorbitol. Castor oil is preferably heated between 50 e 130°C, more preferably 90°C and the cooling of step d) is at between 1 and 10°C, particularly 5°C.

The process of the invention provides also for the addition of an inclusion substance in step b), e.g. β-cyclodextrin.

Examples of manufacturing the composition, formulations of the invention together with tests for determining its active principle release characteristics, its stability and its compliance now follow.

Example 1

In a 1l beaker 60 g of hydrogenated castor oil were heated at about 90°C until a complete solution is obtained. Separately in a polyethylene bag 11.11 g of nicotine polyacrylate, 100 g of sorbitol and 50 g of β-cyclodextrin were mixed. The powder sieved through a sieve of 710 micron was added in the hydrogenated castor oil at 90-100°C. The solution was vigorously stirred in order to avoid the formation of lumps. The mixture was then left at a temperature of 5°C for 1 hour, thereafter it was sieved through the sieve of 710 micron. A granulate, which was mixed with 579.49 g of gum base, 64

g of Wintergreen flavour, 64 g of food sweet flavour, 1.3g of menthol, 3.2 of aspartame, 1.9 g of acesulfame K, 22.5 g of syloid 244 and 22.5 g of talc and, finally, with 20 g of magnesium stearate, is obtained. After careful mixing it was pressed in a Ronchi R18 type pressure machine so as to obtain chewable tablets of 1000 mg. The yield in tablets is above 95%.

The composition of the tablet so obtained is the following:

Nicotine polyacrilate 18%	11.11 mg
(equivalent to 2 mg of nicotine base)	
Gum base for chewing gum	579.49 mg
Hydrogenated castor oil	60 mg
Sorbitol	100 mg
Wintergreen flavour	64 mg
Food sweet flavour	64 mg
Menthol	1.3 mg
Aspartame	3.2 mg
Acesulfame K	1.9 mg
Syloid 244	22.5 mg
Talc	22.5 mg
Magnesium stearate	20 mg
β-cyclodextrin	50 mg
TOTAL	**1000.0 mg**

Example 2

Following the same procedure stated in Example 1 but changing the active principle, the following final formulation was obtained:

Ibuprofen	100 mg
Gum base for chewing gum	1000 mg
Hydrogenated castor oil	200 mg
Sorbitol	300 mg
Mint flavour	100 mg
Aspartame	5 mg
Acesulfame-K	3 mg
Syloid 244	40 mg
Talc	40 mg
Magnesium stearate	35 mg

β-cyclodextrin	100 mg
Isomalt	77 mg
Total	**2000 mg**

Example 3

Following the same procedure stated in Example 1 but changing the active principle, the following final formulation was obtained:

Dextrometorfan hydrobromide	10 mg
Gum base for chewing gum	1050 mg
Hydrogenated castor oil	50 mg
Sorbitol	100 mg
Liquorice flavour	70 mg
mint flavour	40 mg
Aspartame	4 mg
Acesulfame-K	3 mg
Syloid 244	35 mg
Talc	35 mg
Magnesium stearate	30 mg
β-cyclodextrin	100 mg
Isomalt	123 mg
Total	**1650 mg**

IN VITRO RELEASE

A tablet of 1000 mg comprising 2 mg of nicotine was subjected to HPLC (High Pressure Liquid Chromatography) for determining in vitro release of the nicotine by following the procedure stated below.

A device "Water 820" supplied with a column Supelco C18 x 12.5 cm was used. A flow of 1.5 ml/min and wavelength of 254 nm were set. The conditioning of the column was carried out with a mobile phase consisting of ACCN, CH_3COOH, sodium laurylsulfate, sodium acetate and water; retention time was from 3.5 to 5.5 min; sample concentration was 0.04 mg/ml and standard concentration was 0.04 mg/ml in mobile phase.

50 ml of water and a tablet according to the invention were introduced in a suitable bag assuring that all air flows out of it. A chewing machine was operated at "low" speed. 1 ml was collected from the bag at 5, 10, 15, 20, 30 minutes and every time the collected sample was restored with water.

The collected samples were filtered by means of a syringe and 0.45 μ filter and injected on HPLC column which was conditioned as described above.

The release curve plotted in Figure 1 was obtained, from which it can be seen that the release is almost constant between 0 and 30 minutes reaching the complete release at 30 minutes.

IN VIVO RELEASE

Three tablets according to the invention (batch V0018), each comprising 2 mg of nicotine were administered respectively to three adult subjects and the plasmatic levels of nicotine were determined by taking of blood samples. Such *in vivo* release tests were carried out by I.P.A.S. S.A. of Ligornetto (Switzerland). The plasmatic levels obtained at times of taking blood samples are shown in the following Table 1.

Tabella 1

Time (min)	**Conc.** (ng/ml) **Subject 1**	**Conc.** (ng/ml) **Subject 2**	**Conc.** (ng/ml) **Subject 3**
0	0	0	0
10	3.98	2.14	3.32
20	3.63	2.2	3.39
30	3.51	2.81	3.28
40	4.09	2.74	3.61
50	2.71	2.88	3.96
60	3.94	2.74	2.16
75	3.52	3.07	3.4
90	2.85	2.95	3.21
105	2.13	3.05	2.77
120	2.03	2.45	2.41
150	1.53	1.65	2.01
180	1.08	1.69	1.89
210	0.918	1.54	1.45
240	0.991	1.08	1.25
360	0	0	0.582
480	0	0	0

From the concentration data the maximum concentration (Cmax), the time required to obtain it (Tmax) and the area under the curve (AUC) - which was drawn joining the points corresponding to times of taking blood samples - were therefore obtained for each of the tested subjects. (Table 2).

Tabella 2

Subject	**Cmax** (ng/ml)	**Tmax** (min)	**AUC**
Subject 1	4.09	40	8.70
Subject 2	3.07	75	8.60
Subject 3	3.96	50	11.4

From the above data it is clear that nicotine reaches high plasmatic levels within 40-75 minutes confirming good bioavailability and strong absorption of the active principle when the composition of the invention is used.

QUALITY ANALYSIS

One tablet according to the invention (Batch TF 599) comprising 2 mg of nicotine was subjected to quality control according to the specifications stated in Table 3. The results which led to approval of the tablets of the invention are shown in the last column of the table.

Table 3

TEST	SPECIFICATIONS	RESULTS
Pharmaceutical form	Chewing gum	Approved
Form	Round	Approved
Colour	Beige	Approved
Flavour	Wintergreen	Approved
Length-Width	19.5 x 11.5 mm	19.5 x 11.5 mm
Height	4.5-5.5 mm	4.9 mm
Hardness	5 - 15 Kp	10 Kp
Medium weight	950-1050 mg	1005 mg
Water content	≤ 2%	0.59%
Nicotine content	1.9 - 2.1 mg 95 - 105%	2.03 mg 101.5%

STABILITY CONTROL

The product of the invention comprising 2 mg of nicotine (batch: TF 599) was studied in order to determine the stability for 6 months at 40-75% of humidity, packaged in blisters of the following materials: PVC, PVC + ALU, PVDC and PVDC + ALU. The tablets according to the invention resulted in conformity with chemical and physical controls and therefore stable in the studied conditions.

From the stability plan a stability for 12 months at 30°C - 60% of humidity and for 24 months at 25 - 60% of humidity was inferred.

COMPARATIVE COMPLIANCE STUDY

A comparative study between a medicated chewing gum with nicotine according to the invention and a comparative formulation, which is commercially available as NICORETTE® manufactured by Pharmacia-

Upjohn and does not contain the coating mixture according to the invention, was carried out. Six volunteers were periodically examined.

All the volunteers defined the taste of the formulation test as being better and, during the chewing, nobody felt irritation which was noticed for the comparative formulation.

It is clear that many variations and/or modifications of elements with functionally equivalent others, such as substitutions of soluble and insoluble elements with functionally similar substances, may be carried out to the foregoing detailed description and preferred embodiments without departing however from its scope as defined in the appended claims.

CLAIMS

1. Composition for medicated chewing gums, characterized by the fact that the particles of the active principle dispersed in the gum are coated by a mixture consisting of a hydrosoluble element and a water insoluble element, said coating allowing a gradual and controlled release of the principle to be obtained.

2. Composition according to claim 1 wherein the active principle is selected from the group consisting of nicotine, ibuprofen, paracetamol, D-metorfan, dimenhydrinate, ginger, 1-ascorbic acid (vitamin C), acetylcysteine, ephedrine, D-pseudoephedrine, valerian, ranitidine, chlorexidine, tibenzonium iodide.

3. Composition according to claim 2 wherein the active principle is nicotine, preferably nicotine polyacrilate.

4. Composition according to any one of the preceding claims wherein the water insoluble element is an oil or other insoluble substances selected from the group consisting of plant hydrogenated oils, paraffin, beeswax, stearic alcohol , stearyl alcohol, cetyl alcohol, cetostearyl alcohol.

5. Composition according to claim 4 wherein the insoluble element is hydrogenated castor oil.

6. Composition according to any one of the preceding claims wherein the soluble element is a carbohydrate or a polyhydric alcohol.

7. Composition according to claim 6 wherein the soluble element is selected from the group consisting of sorbitol, sucrose, lactose, glucose, fructose, mannitol, xilitol, isomalt, more preferably sorbitol.

8. Composition according to any one of the preceding claims wherein the active principle is between 0.1 and 20% by weight, preferably 1.11% of the total composition.

9. Composition according to any one of the preceding claims wherein if the amount of the active principle is defined as Z, then the insoluble element is between 1Z and 10Z.

10. Composition according to any one of the preceding claims wherein if the amount of the active principle is defined as Z, then the soluble element is between 2Z and 20Z.

11. Composition according to any one of the preceding claims wherein if the active principle is nicotine polyacrylate in amounts of 1.11% by weight of the total composition, then the insoluble element is between 1.11% and 11.1% by weight, preferably hydrogenated castor oil in amounts of 6.0% by weight of the total composition.

12. Composition according to any one of the preceding claims wherein if the active principle is nicotine polyacrylate in amounts of 1.1% by weight of the total composition, then the hydrosoluble element is between 2.22% and 22.2%, preferably sorbitol in amounts of 10% by weight of the total composition.

13. Composition according to any one of the preceding claims characterized by the fact that the gum base is selected each time according to the health regulations of the countries where the product is consumed.

14. Composition according to any one of the preceding claims comprising additives selected from the group consisting of flavours, sweeteners, dehydration agents, pH stabilizers, inclusion agents, lubricants, etc.

15. Composition according to claim 14 wherein the flavour is Wintergreen.

16. Composition according to claim 14 wherein the inclusion agent is β-cyclodextrin.

17. Composition according to any one of claims 14-16 wherein the sweeteners are selected from the group consisting of acesulfame K, aspartame, saccharin, cyclamates, neoesperidine, maltol, ethylmaltol.

18. Composition according to any one of the preceding claims wherein the pH of the composition is between 5 and 10, preferably 7.5.

19. Process for obtaining the medicated chewing gum having the composition according to any one of claims 1-18 characterized by the following steps:

a) heating the insoluble element until a complete solution is obtained;

b) mixing the soluble element with the active principle;

c) pouring the mixture of step b) in the solution of the insoluble element;

d) cooling the mixture so obtained and mixing with the gum base and the additives; and

e) pressing at a temperature not above room temperature.

20. Process according to claim 19 wherein in step a) the insoluble element is hydrogenated castor oil heated between 50 e 130°C, more preferably 90°C.

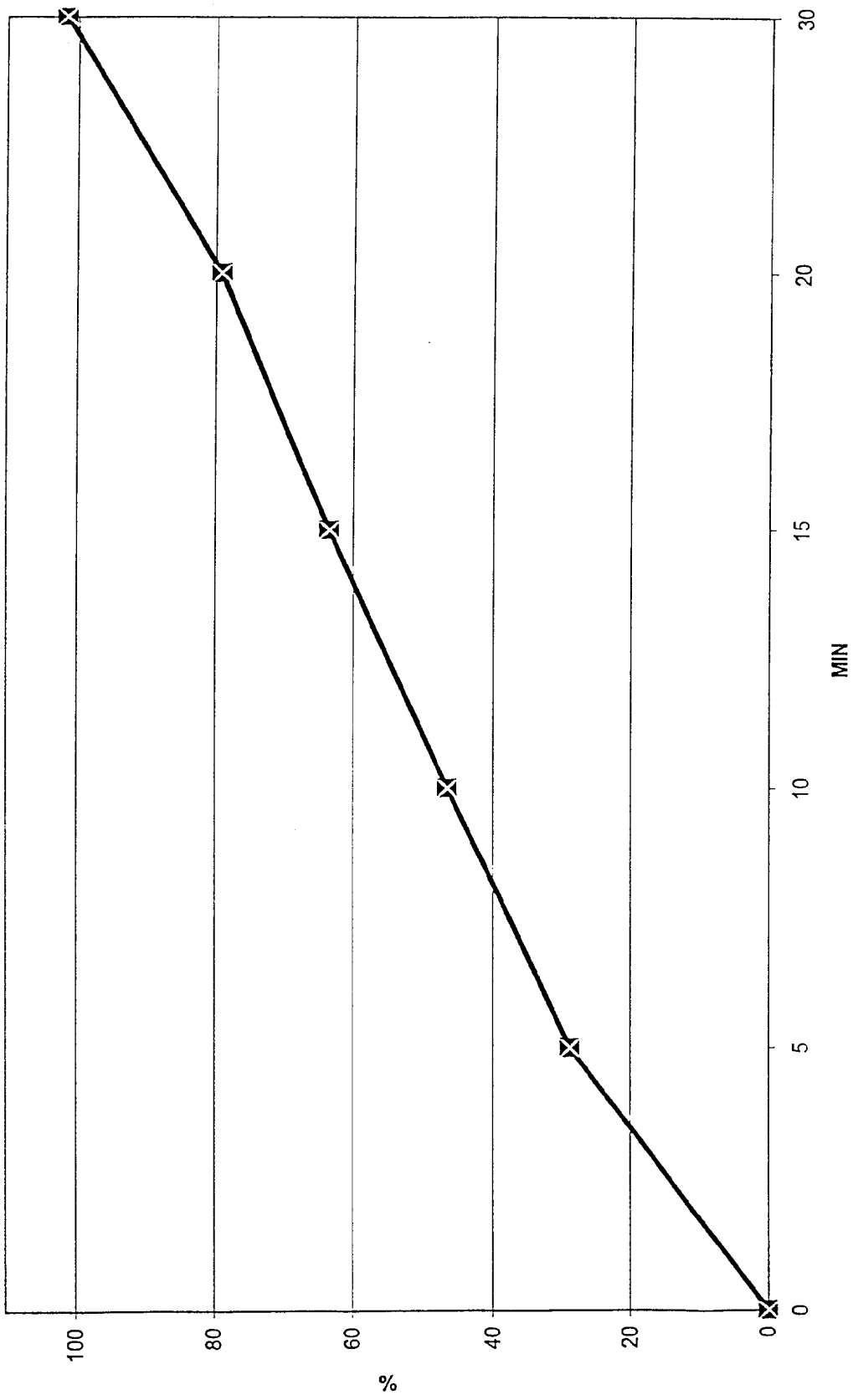
21. Process according to any one of claims 19 and 20 wherein the cooling is at between 1 and 10°C, particularly 5°C in step d).

22. Process according to any one of claims 19-21 wherein the inclusion agent, preferably β-cyclodextrin, is also mixed in the step b).

23. Tablet of medicated chewing gum having the composition according to claim 1 and obtained according to claim 19 characterized by a stability at temperature of 40 °C and 75% of humidity.

24. Use of the chewing gum tablet with the composition according to claim 1 for the administration through the oral cavity.

25. Use of the chewing gum tablet with the composition according to claim 3 in the treatment for giving up smoking.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INTERNATIONAL SEARCH REPORT

Inter ›nal Application No
PCT/EP 99/07917

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/00 A61K9/68

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 934 596 A (WARNER-LAMBERT) 21 August 1963 (1963-08-21) claims	1-25
A	WO 84 03201 A (WRIGLEY) 30 August 1984 (1984-08-30) claims	1-25
A	EP 0 177 368 A (WARNER-LAMBERT) 9 April 1986 (1986-04-09) claims	1-25
A	US 4 885 175 A (S.E.ZIBELL) 5 December 1989 (1989-12-05) claims	1-25

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter onal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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